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Award Number: DAMD17-02-1-0324

TITLE: Monitoring the Response of Chemotherapy on Breast Cancer Tumors by Photon Migration Spectroscopy

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REPORT DATE: June 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
01/06/2005	Annual Summary	6 May 04 - 5 May 05

4. TITLE AND SUBTITLE
Monitoring the Response of Chemotherapy on Breast Cancer Tumors by Photon Migration Spectroscopy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-1-0324

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of California, Irvine
Irvine, CA 92697-1875

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. The optimal intensity and duration of the neoadjuvant chemotherapy regiment for LABC still remains controversial due to the difficulty of evaluating response to the treatment. The goal of this project is to use Photon Migration Spectroscopy (PMS) as a new modality to monitor the response of breast tumor to neoadjuvant chemotherapy. We measured 29 patients and PMS showed excellent sensitivity to the crucial early functional changes in breast tissue subjected to neoadjuvant chemotherapy. We defined a novel new "Optical Index" which incorporates all the optical parameters into a single easy to understand value which better describes the response of the tumor to the neoadjuvant chemotherapy. By using PMS and the optical index we are able to distinguish between subjects responding to neoadjuvant chemotherapy versus the non responders. Conclusion: By using Photon Migration Spectroscopy we have been successful in monitoring the response of breast cancer to neoadjuvant chemotherapy and identifying responders vs non-responders.

15. SUBJECT TERMS
Neoadjuvant, Chemotherapy, Photomedicine, Laser Medicine

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (include area code)
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INTRODUCTION

Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. LABC represents 5-20 % of all newly diagnosed breast cancers in the United States with a higher incidence in medically underserved areas. Over the years, treatment for LABC has been evolving from performing a radical mastectomy to the use of pre-operative neoadjuvant chemotherapy followed by mastectomy or breast conservation therapy. However despite aggressive local therapy, the long term survival outlook is still dismal for these patients. Key factors for these poor outcomes are that the optimal intensity and duration of neoadjuvant chemotherapy for LABC remains controversial due to the difficulty of evaluating response to therapy.

Presently, response to neoadjuvant chemotherapy treatment is determined by a) serial physical exams; b) mammograms and or c) ultrasound measurements. Yet many recent studies have revealed significant discrepancies between the clinical assessment of response based on these modalities and the final pathologic assessment of response found in post therapy surgical specimens. The final pathological response is very important because patients achieving a complete pathologic response have a longer survival compared to those patients who have residual microscopic disease at the time of surgery as reported in the NSABP B18 trial. Subsequent studies have also suggested that achieving a complete pathological response can also be a surrogate for eradicating micrometastases, which translates into a longer survival outcome.

The goal of this project is to use Photon Migration Spectroscopy (PMS) as a new modality to monitor the response of breast tumor to neoadjuvant chemotherapy.

BODY

Statement of Work Accomplishments

SPECIFIC AIM 1: DEVELOP TRIAL PROTOCOL

1/2. *Develop subject tracking system / Design Database*

These tasks have been completed. (Last report 2003)

SPECIFIC AIM 2 : TRAINING

1. *Audit Bioengineering ,Physics and Photomedicine courses on campus to enhance fundamental knowledge of Photon Migration Spectroscopy*

This task has been completed.

I am still continuing to attend the Beckman Laser Institute lecture series to keep current with the new developments in the field of optics.

2. *Rotation in Pathology department to learn slide preparation and immunohistochemical staining*

This task has been completed. (Last report 2003)

3. *Enrollment in Ultrasound training course*

This task has been completed. (Last report 2004)

SPECIFIC AIM 3: ENROLLMENT OF SUBJECTS

1. *Start enrollment of subjects*

This task continues. Thus far we have enrolled a total of 29 subjects. Four more subjects will be enrolled before the end of June 2005. Since last report no subject has withdrawn from the study.

See **Appendix A for details**

2. *Scheduling of subsequent measurement dates*

This task continues with remaining subjects. We have been concentrating on obtaining more readings in the initial first and third week of the chemotherapy regiment. This was after we analyzed the preliminary data. A more detailed explanation is included in the conclusion section..

SPECIFIC AIM 4 : TUMOR MEASUREMENTS

1. *Obtain Pre - Post Chemotherapy Photon Migration Spectroscopy measurements*

This task continues with remaining subjects.

2. *Obtain Pre - Post Chemotherapy Ultrasound measurements*

This task continues with remaining subjects.

SPECIFIC AIM 5 : CORRELATION OF PMS MEASUREMENTS WITH ULTRASOUND AND HISTOLOGY DATA

1. *Correlation of Ultrasound data and PMS data*

This task is completed

2. *Analysis of histology data with immunohistological staining of post surgical specimens*

This task is completed

SPECIFIC AIMS 6 : FINAL ANALYSIS AND REPORT

1. Analysis of all data

This task is completed.

2. *Preparation of manuscript*

This task is completed

KEY RESEARCH / CAREER ACCOMPLISHMENTS

1. Development of database for data management
2. Development of trial protocol
3. Obtaining IRB approval of protocol
4. Audit of Photomedicine / Optic courses
5. Rotation in Pathology lab
6. Enrollment in Ultrasound training course
7. Enrollment of subjects
8. Scheduling of subsequent measurement dates
9. Obtain Pre - Post Chemotherapy Photon Migration Spectroscopy measurements
10. Obtain Pre - Post Chemotherapy Ultrasound measurements
11. Correlation of Ultrasound data and PMS data
12. Analysis of histology data with immunohistological staining of post surgical specimens
13. Analysis of all data
14. Preparation of manuscript

REPORTABLE OUTCOMES

The following is a list of grants, awards, presentations, papers and abstracts

1. Grants

A) *ANGIOGENSIS IN HYPERPLASIA TO IN-SITU BREAST CANCER*

9WB-0020 Su (Hsiang co-PI)	7/1/2003 to 6/30/2005
California BCRP	$250,000 Total

B) *Breast Cancer Functional Imaging with Optics and MRI*

10EB-0208 Tromberg (Hsiang co-PI)	7/1/2004 to 6/30/2007
California BCRP	$500,000 Total

C) *NITRO grant: "A Network for Translational Research in Optical Imaging: Multi-Dimensional Diffuse Optical Imaging in Breast Cancer*

CA-03-002 Tromberg (Hsiang co-PI)	9/1/2003 to 8/31/2008
National Institute of Health	$7.1 million Total

2. Awards

2005 Grants in Aid for Academic Clinicians Award

UCI	4/1/2005 to 4/1/2007
	$50,000 per year

3. Presentations

2005 **Hsiang D** – SPIE 2005 "Defining the role of Optical methods in Breast Cancer Detection" *Photonic West 2005*, San Jose CA – Invited Panel member

2004 **Hsiang D**, Butler J " Update on Optics in Breast Biology " 4th *Annual Chao Family Comprehensive Cancer Retreat* , Palms Spring CA , Presentation

2003 Jakubowski D.B.,Cerussi A.E.,Bevilacqua F.,Shah N.,Tromberg B.J.,**Hsiang D.**,Butler J., and Holcombe R.F., "Monitoring breast tumor response to chemotherapy with broadband near-infrared tissue spectroscopy," *Spring Topical Meeting, Optical Society of America*, Biomedical Optical Spectroscopy and Diagnostics, Miami, FL, Presentation

2002 **Hsiang D.**,Cerussi A.,Jakubowski D.,Baick C.,Tromberg B., and Butler J. "Monitoring the response of breast cancer tumors to chemotherapy with photon migration spectroscopy" *American College of Surgeon, Southern California Chapter*, Santa Barbara, CA Presentation

3. Papers

2005 **Hsiang D**,Shah N, Yu H, Su M, Cerussi A, Butler J, Baick C, Mehta R, Nalcioglu, Tromberg B, " Coregistration of Dynamic Contrast Enhanced MRI and Broadband Diffuse Optical Spectroscopy for Characterizing Breast Cancer ", Technology in Cancer Research and Treatment – Accepted June 2005

2004 Jakubowski D.B., Cerussi A.E.., Bevilacqua F., Shah N., **Hsiang D.**, Butler J., and Tromberg B.J., "Monitoring neoadjuvant chemotherapy in breast cancer using quantitative diffuse optical spectroscopy: a case study", Journal of Biomedical Optics, 9(1), 230-238 (2004).

2004 Shah N, Cerussi AE, Jakubowski D, **Hsiang D**, Butler J and Tromberg BJ. "The role of diffuse optical spectroscopy in the clinical management of breast cancer". Disease Markers. 2003-2004;19(2-3):95-105.

2004 Shah N, Cerussi AE, Jakubowski D, **Hsiang D**, Butler J and Tromberg BJ. "Spatial variations in optical and physiological properties of healthy breast tissue" .Journal of Biomed Opt. 2004 May-Jun;9(3):534-40.

4. Abstracts

2005 Shah N, Cerussi, **Hsiang D**, Butler J, Tromberg BJ, M Su, and O Nalcioglu "Combined Diffuse Optical Spectroscopy and Magnetic Resonance Imaging for Assessment of Breast Tumor Response to Neoadjuvant Chemotherapy". June 2005 European Conference on Biomedical Optics, Neue Messe, Munich Germany

2004 Mehta R, Schubbert T, **Hsiang D**, Su L, Carpenter P, Holcombe R, Butler J, and Baick C. "High pathological complete remission rate following neoadjuvant taxane,carboplatin and trastuzumab therapy after doxorubicin and cyclophosphamide in Her-2 positive breast cancer patients" . 27th Annual San Antonio Breast Conference Symposium Dec 2004 San Antonio TX

2004 Su M, Yu H, Mehta R, Carpenter P, **Hsiang D**, Butler J, Baick C and Nalcioglu O, "MRI Monitoring of Neoadjuvant Chemotherapy in Breast Cancer: Association of Early and Final Responses in AC followed by Taxol ± Herceptin Regimen with MRI Morphological Patterns" International Society of Magnetic Science in Medicine, May 2004 Miami FL

4. Collaborations

A) **Update** – a Project Program Grant (PPG) was submitted with the Epidemiology Division at UCI for Evaluating High Risk Breast Cancer Women. There were a total of 4 projects in this grant. I am the Principle Investigator on Project 3. (Breast Tissue Optical Properties by Laser Emission Skin Scanner : Project 3 of PPG Etiology and Detection of Breast Cancer in a Family Cohort - Estimate 3-4 Million for PMS section - Total PPG 12 Million). Unfortunately the PPG was not funded even after the resubmission attempt The PPG received good scores but not high enough for funding.

B) **New** – Due to the PPG not being funded. I have submitted a RO1 based on Project 3.

C) **Update** – the collaborative project with UCSF by using the Photon Migration Spectroscopy concurrently with MRI scanning of subjects undergoing Neoadjuvant chemotherapy is going very good. We are sharing information and there has been very exciting data generated from this collaboration. Thus far the correlation data seems to match up. UCSF was able to submit an abstract for the 2004 San Antonio Breast Meeting based on this data.

CONCLUSIONS

The conclusion will be addressed by 2 sections 1) Career Development 2) Photon Migration Spectroscopy results

1) **Career Development**

Upon reflection, I feel with the support of the Career Development Award (CDA) I was able to accomplish several very important projects over the last 3 year. The CDA was pivotal in providing the protected time I need to be able to obtain other grants and collaborate with other investigators. This is evident in the 4 grants 9WB-0020 Angiogenesis In Hyperplasia To IN-SITU Breast Cancer grant ; 10EB-0208 Breast Cancer Functional Imaging with Optics and MRI grant and the very large CA-03-002 NITRO grant: "A Network for Translational Research in Optical Imaging: Multi-Dimensional Diffuse Optical Imaging in Breast Cancer" grant. Hopefully I will continue to have success in obtaining more grants and in the future obtain a RO1 grant.

In the area of publishing, I have co-authored several papers and was first author on one paper which was recently accepted. My next area of emphasis is to become more active in publication. By working on the last several papers I have learned the "art of writing" scientific papers and will be aggressively publishing the near future with the data I have obtained thus far.

I was recently awarded a " translational" award (Grants in Aid for Academic Clinicians Award) from my own institution which mimics the CDA in its support of providing protected time for young physician researchers to develop research careers. This will be continuing support for my research career.

2) **Photon Migration Spectroscopy Results**

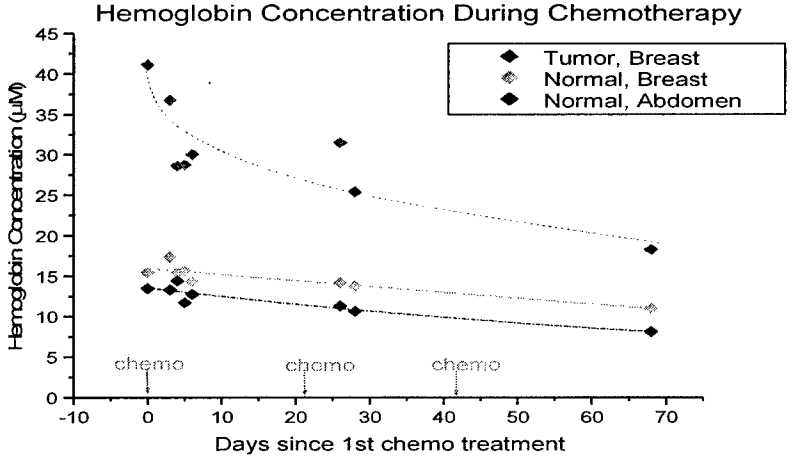
Optimal management of patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. The optimal intensity and duration of the neoadjuvant chemotherapy regiment for LABC still remains controversial due to the difficulty of evaluating response to the treatment. The goal of this project is to use Photon Migration Spectroscopy (PMS) as a new modality to monitor the response of breast tumor to neoadjuvant chemotherapy.

When we started the project neoadjuvant chemotherapy was just being introduced as a new treatment option for large un-resectable locally advanced breast cancer. Yet over a short period the field of neoadjuvant chemotherapy for breast cancer has expanded tremendously to include tumors as small as 2 cm in size. Yet to date there still lacks an accurate method of measuring the neoadjuvant chemotherapy response. There are many papers published on the discrepancy of measured response based on the traditional physical exam, ultrasound, mammogram and MRI.

From the data obtained in this study, PMS has the promise to a better modality than the traditional methods listed previously. The reason is that PMS measures the metabolic changes in the breast whereas the other modalities measure to the structural changes. In addition, it is well known that metabolic changes usually precede a structural change.

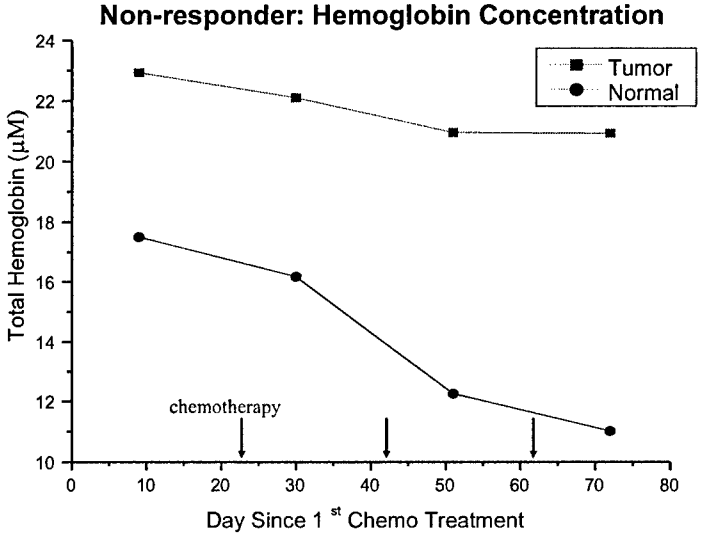
In this study, we measured 29 patients and PMS showed excellent sensitivity to the crucial early functional changes in breast tissue subjected to neoadjuvant chemotherapy. We based our monitoring on the strongest optical signal which was hemoglobin.

The typical monitoring graph is as follows (plot of hemoglobin over time)

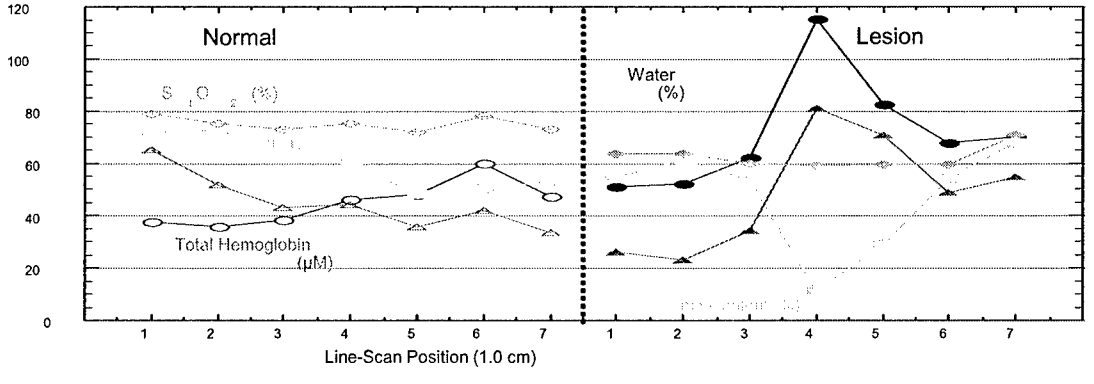


There is usually a large drop initially which tapers to stable value over time. This is seen in all the " responders" – this defined as a change greater than 50% any axis measured by physical exam or ultrasound (U/S) or mammogram.

For the non- responders the typical graph is as follows



When compared with other measured parameters using traditional physical exam, U/S and mammogram on the same patients, there was no correlation. Hence, just following the local breast hemoglobin concentration changes over time, we were able to monitor the chemotherapy effects on the breast. All the responders had the same graph when we plotted hemoglobin vs time. The same was true for the non responders (no large drop in hemoglobin) . But with PMS there were other physiological components we could measure. The other optically active components were water ,lipids, and hemoglobin oxygen saturation. Below is a typical graph of the other components measured by PMS over the breast tumor. The breast tumor location is in the center at position 4.



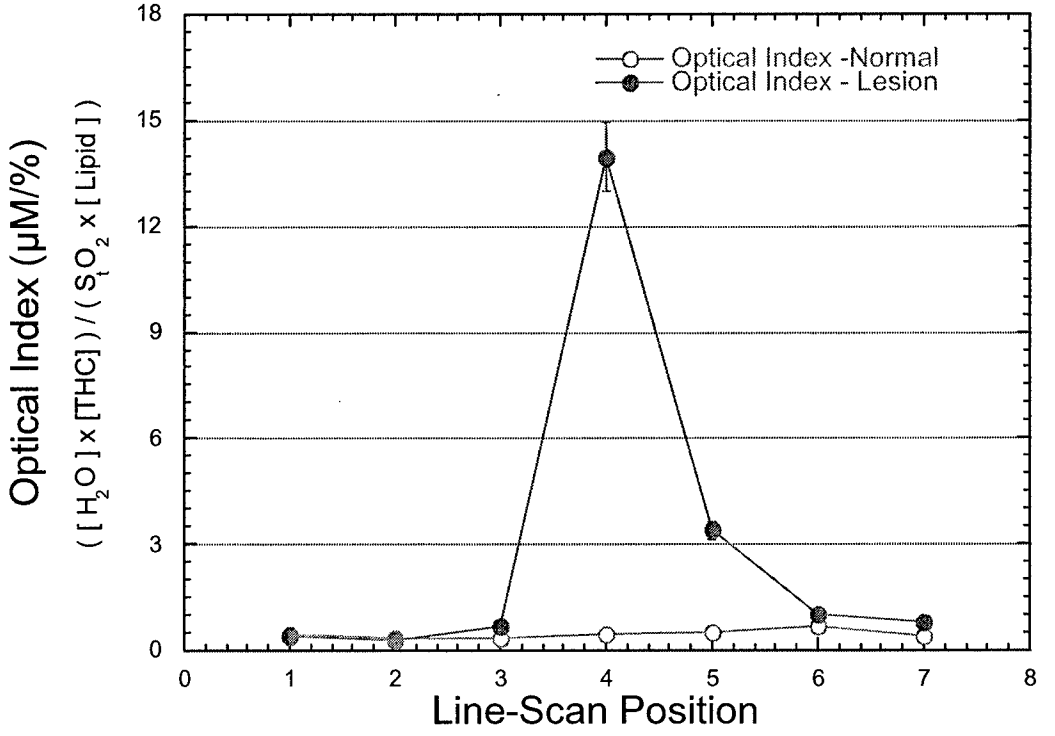
Since there were 3 additional components to consider we defined a novel "Optical Index" which incorporates all the optical parameters into a single value.

The Tissue Optical Index (TOI) is described as

$$\text{TISSUE OPTICAL INDEX} = \frac{\text{Water } (H_2O) \textbf{ X } \text{Total hemoglobin}}{\text{Lipid } \textbf{X} \text{ Oxygen Saturation } (S_tO_2)}$$

The signal to noise ratio (noise defined as normal tissue) was greatly enhanced.

The same data plotted by using TOI is shown below.



By measuring the tissue optical index we are able to better distinguish between subjects responding to neoadjuvant chemotherapy versus the non responders.

The data from the histological studies for residual study has not worked out well. There is a fundamental flaw in comparing histology slides with PMS. The reason is due to sample heterogeneity. Breast cancer tumors are not homogeneous thus there can be tremendous variability depending on where the tissue section is obtained. PMS on the other hand is diffuse optics, which means that it takes an average of the tissue signal under interrogation. The results we obtained had no correlation. I think to overcome this problem. We will have to resort to an animal model where the size of the tumor can be controlled and the heterogeneity is less. We have started a collaborative effort with another basic science investigator (Stuart Nelson) to develop a working animal model to further study this problem.

All the above data is being prepared in a manuscript to be submitted to a journal to be published.

One very interesting observation that is currently being analyzed is has that initial PMS measured changes might be used in a predictive of final pathological response. The initial changes measured in the first 72 hours after receiving the chemotherapy was found to correlate with the final pathological result. The subjects with a complete or near complete pathological response had very large changes measured in the slope of the response whereas the subjects with partial response had a more moderate slope. The predictive analysis is currently ongoing. This is could be a very important finding clinically. The reason is that as neoadjuvant chemotherapy regiments move to a shorter time intervals as seen in newer protocols incorporating " Dose Dense " protocols, there will be a critical need for an ultra fast measurement of chemotherapy response. The traditional methods will be too slow and as demonstrated not accurate.

Photon Migration Spectroscopy can be used in monitoring the response of breast cancer to neoadjuvant chemotherapy and identifying responders vs non-responders.

Appendix A

Subject Data

SID	MR#	MRI study	Race	BD	Menopausal	lesion	chemo Rx Treatment
1	1725549	unk	asian	10/5/1954	pre-m	RUI at 1 o'c 2.5x8x1.3 cm	6/02-12/02-2 AC pre-op, 4 taxotere post-op
2	1728491	unk	asian	1/20/1947	post-m	LUO at 2o'c 2.1x1.2x1.0 cm	7/02-1/03 4AC and 4 Taxotere
3	1742493	unk	asian	7/10/1949	post-m	LUO at2 o'c 5x5 cm	8/02-1/03 4AC and 4 Taxotere
4	1658696	unk	islander	6/19/1955	post-m	RUO at11 o'c 4.8x4.7x4.0cm	11/02-4/03 4AC and 4 Taxotere
5	1753460	unk	hispanic	10/29/1937	post-m	LLO at 2o'c 18x16mm	12/02-4/03 3 AC and 4Taxotere
6	1759566	unk	hispanic	10/23/1969	post-m	RUO at 12o'c 11x10cm	12/02-7/03 2AC,4TX,13CPH
7	1759577	unk	hispanic	3/14/1964	post-m	RUOat 12o'c1.9x2.1cm	4AC,4 TX
8	1759670	unk	hispanic	5/2/1972	pre-m	RUI at 12'o'c6X6cm	1/03-6/03 4AC and 4 Taxotere
9	1792490	unk	white	3/25/1946	post-m	LUI at 9'o'c 1.2x.8x1cm	7/03-11/03 3 AC and 11 CTH

10	1728002	unk	asian	1/12/1964	pre-m	RLO at 6'o'c 3x2.8x1.2cm	7/03-10/03 4AC and 3 Taxol
11	1794682	unk	hispanic	9/26/1960	pre-m	LUI at 12'o'c 2.5 cm mass	8/03-AC/Taxol
12	1811544	unk	hispanic	3/2/1972	pre-m	LUI at 930o'c 7x7 cm	AC-9/30-11/12/03 Taxol-11/26/03-1/8/04
13	1813315	4/27/04.	white	11/4/1953	post-m	9/10/03 US-LUI at11'o'c 46mm	AC-10/21-12/23/03 Taxol-1/21-4/20/04
14	1824608	n/a	black	6/15/1969	pre-m	1/13/04 RLO at 5-8o'c 5cm>nipple size 6x4 cm	AC-2/12-4/7/04 Taxol-5/19,6/16/04
15	1833152	n/a	asian	4/9/1957	pre-m	LLI at 6 o'c11.3x8.2x3.3 cm	n/a
16	1797822	4/29/04 7/28/04	white	2/9/1940	post-m	12/29/03 LUO at 3 o'c size10mm 4cm >nipple	AC-2/27-3/29 Taxol 4/9-7/23/04
17	18438291	none	white	8/9/1944	post-m	2/23/04 RLO at 8o'c size 31mm 10cm >nipple	AC-4/27-5/11/04 Taxol-5/25-8/3/04
18	1810529	4/22/04 5/11/04 9/8/04	hispanic	5/21/1963	peri-m	3/11/04 ultrasound LUO at 2o'c 11 cm > nipple size 7mm	chemo protocol #04-3517 UAC-4/28-6/9/04 Taxol-6/23-9/10/04
19	925833		hispanic	2/9/1963	peri-m	LUO at 2o'c 9 cm> nipple	no pre treatment

20	1856640	10/20/4 11/17/04 1/12/05 3/9/05	white	12/30/1940	post-m 1995	6/1/04 ultrasound RUO at 930 o'c 7cm>nipple size 3.8cm	chemo protocol # 2004-3517 UCI # 03-70
21	1842938	8/11/04 8/25/04 10/6/04 12/8/04 1/12/05	white	9/13/1956	pre-m	7/2/04-RUO at 10 o'c 5-6cm >nipple 2.4x1.7x2.7cm	Chemo protocol #04-3517 AC-8/17-9/28 Taxol-10/12- 12/21
22	1866486	9/8/04 10/13/04 11/24/04 2/16/05	hispanic	10/6/1966	pre-m	6/04 ultrasound in Costa Rica LUO6x2.5cm at UCI 9/14-2.4 cm at 11-1230 o'c	chemo protocol #04-3517 AC-9/29-11/11 Taxol-11/30- 2/8/05
23	1870737	10/6/04 10/27/04 12/1/04 3/9/05	white	1/22/1954	post-m 1996	9/24 ultrasound LUO at 330 o'c 4cm>nipple 0.7x0.5x5.4	chemo protocol #04-3517 AC-10/14-11/29 Taxol-12/9- 2/21/05
24	1337375	clinical 2/8/05	white	3/19/1943	post-m 1989	LUO 2cm appox 5.5 from nipple	chemo protocol # 04-3517 AC- 1/6-2/24/05 Taxol-3/17- ongoing
25	1886770	1/19/05 2/9/05	white	10/27/1948	post-m 1988	1/6-ultrasound RUO-1030 o'c4cm from nipple 12.0x9.0x10mm	chemo protocol #04-3517 AC- 2/3-2/17 Taxol-3/3 ongoing
26	15877908	1/19/05 2/9/05	hispanic	6/4/1973	pre-m	12/27- ultrasound RUO-1000 o'c 8 cm from nipple size 2.5 cm	chemo protocol #04-3517 AC-2/1-3/15 Taxol-3/23 on going
27	1880463	1/19/05 2/23/05	white	1/9/1952	post-m 1999	LUO ultrasound 1/25/05 -3.2 cm at 2 o'c 6cm from the nipple	chemo protocol #04-3517 AC- 2/9,2/22 Taxol- 3/8-ongoing

28	1899683	3/30/05-	white	11/5/1958	post-m	mamo 3/23 US 4/6 at 10 o'c 1.7x1.4x1.3cm	chemo protocol # 04-3517 AC-4/21-ongoing
29	19097577	6/8/05,	white	3/26/1948	pos-m	mammogram 4/5/05 at 2o'c 2.5cm	chemo protocol # 04-3517 AC-5/31/05- ongoing

The following are copies of papers and abstracts

Papers

1. **Hsiang D**,Shah N, Yu H, Su M, Cerussi A, Butler J, Baick C, Mehta R, Nalcioglu, Tromberg B, " Coregistration of Dynamic Contrast Enhanced MRI and Broadband Diffuse Optical Spectroscopy for Characterizing Breast Cancer ", Technology in Cancer Research and Treatment – Accepted June 2005

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Abstracts

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